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Therapeutic Class Review
5-HT$_3$ Receptor Antagonists

Overview/Summary

Type 3 serotonergic (5-HT$_3$) receptor antagonists are Food and Drug Administration (FDA)-approved for the treatment of chemotherapy-induced nausea and vomiting (CINV), postoperative nausea and vomiting (PONV), and/or radiation-induced nausea and vomiting (RINV). Although the medications in this class vary slightly in their FDA-approved indications, expert guidelines do not generally differentiate between them and consider them equally effective.[1-26] The mechanism of action for these agents results from the blockade of 5-HT$_3$ receptors in both the gastric area and the chemoreceptor trigger zone in the central nervous system. By blocking these receptors, these medications disrupt the signal to vomit and reduce the sensation of nausea.[4,21] CINV frequently requires multiple-drug therapy. Along with corticosteroids, 5-HT$_3$ receptor antagonists are considered the main pharmacologic interventions.[1,4-11]

In general, the 5-HT$_3$ receptor antagonists are considered equally effective when given at equipotent doses. However, there are some differences in regards to duration of action, metabolic pathways, routes of administration and dosing schedules. All of the 5-HT$_3$ receptor antagonists are available by both the oral and injectable routes, with the exception of palonosetron, which is only available by injection at this time. In August 2008, the manufacturer of palonosetron received FDA approval to market an oral formulation. In September 2008, the manufacturer of granisetron received FDA approval to market a transdermal formulation. Both of these products are not included in this review. Granisetron and ondansetron are the only 5-HT$_3$ receptor antagonists that are available generically.

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Dolasetron (Anzemet®)	5-HT$_3$ receptor antagonist	-
Granisetron (Kytril®, Granisol®)	5-HT$_3$ receptor antagonist	✔
Ondansetron (Zofran®, Zofran ODT®)	5-HT$_3$ receptor antagonist	✔
Palonosetron (Aloxi®)	5-HT$_3$ receptor antagonist	-

Indications

Table 2. Food and Drug Administration (FDA) Approved Indications[27-30]

Generic Name	Chemotherapy-Induced Nausea and Vomiting (CINV)	Radiation-Induced Nausea and Vomiting (RINV)	Postoperative Nausea and Vomiting (PONV)
Dolasetron	✔		✔
Granisetron	✔	✔	✔
Ondansetron	✔	✔	✔
Palonosetron	✔ *		✔

*Prevention of acute and delayed CINV.

Pharmacokinetics

All of the 5-HT_3 receptor antagonists are metabolized to some degree via the cytochrome P450 enzymatic pathway. Dolasetron is metabolized by carbonyl reductase into hydrodolasetron, an active metabolite. Hydrodolasetron and palonosetron are primarily metabolized by cytochrome CYP2D6. Ondansetron is metabolized via CYP1A2, CYP2D6 and CYP3A4 with CYP3A4 the primary metabolic pathway. Granisetron is metabolized primarily by CYP3A4.[27-31] It has been suggested that a polymorphism at CYP2D6 may result in faster metabolism and hence lower efficacy of 5-HT_3 receptor antagonists metabolized by this route.[32-35] The clinical significance of this finding has not been demonstrated. The pharmacokinetic parameters for the 5-HT_3 receptor antagonists are summarized in Table 3.

Table 3. Pharmacokinetics[1,27-32]

Generic Name	Duration (hours)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Dolasetron, injection Dolasetron, oral	No data	53 (Hydro-dolasetron)	Yes; Hydro-dolasetron	Dolasetron:<10 minutes Hydrodolasetron: 7.3
Granisetron, injection Granisetron, oral	>24	12	None	9
Ondansetron, injection Ondansetron, oral	9	5	None	3-5.5
Palonosetron, injection	>24	40	None	40

Clinical Trials:

Numerous clinical trials have compared the agents in this class to other medications in the same class, other medications with the same indications, and placebo. In general most studies used adult patients, with a few clinical trials evaluating the use of these agents in children. The results of these trials have varied slightly in efficacy of a particular agent but overall no particular agent was found to be consistently more efficacious than another agent.

For each indication the 5-HT_3 receptor antagonists were studied in specific populations. The inclusion criteria of these studies were designed to create a study population that would mimic the normal population that uses these medications. The Food and Drug Administration-approved indications for a particular 5-HT_3 receptor antagonist should guide selection of one agent over another since studies do not conclusively show a difference between the agents in the class.

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Chemotherapy-Induced Nausea and Vomiting (CINV)				
Eisenberg et al[37] Dolasetron 100 mg IV vs palonosetron 0.25 mg IV vs palonosetron 0.75 mg IV	DB, MC, PG, RCT Patients receiving moderately emetogenic chemotherapy, study drug given 30 minutes before chemotherapy, dexamethasone could be added 15 minutes before chemotherapy	N=592 5 days	Primary: Complete response (no emetic episodes and no need for rescue medication) during the first 24 hours after chemotherapy Secondary: Complete response during hours 24-120	Primary: The proportion of patients with complete response was not statistically different between the two palonosetron doses and dolasetron (palonosetron 0.25 mg 63% vs dolasetron 100 mg 52.9% [97.5% CI, -1.7% to 21.9%; *P*=0.049]), (palonosetron 0.75 mg 57.1% vs dolasetron 100 mg 52.9% (97.5% CI, -7.7% to 16.2%; *P*=0.412)]. Note: Significance was *P*<0.025 using the one-sided Fisher exact test. Secondary: Complete response with palonosetron 0.75 mg and 0.25 mg were significantly higher in the delayed phase (hours 24-120) compared to dolasetron (palonosetron 0.75 mg vs dolasetron 100 mg; *P*<0.001 and palonosetron 0.25 mg vs dolasetron 100 mg; *P*=0.004). Adverse effects were mild and similar for all 3 groups.
Lofters et al[38] Dolasetron 2.4 mg/kg IV followed by dolasetron 200 mg PO (arm 1) vs dolasetron 2.4 mg/kg IV and dexamethasone 8 mg IV followed by dexamethasone 8 mg PO (arm 2) vs dolasetron 2.4 mg/kg IV and dexamethasone 8 mg IV	DB, PG, RCT Patients receiving 7 days of moderately emetogenic chemotherapy	N=696 7 days	Primary: Control of nausea and vomiting in the first 24 hours, complete response was no episode of emesis Secondary: MNS based on a visual analog scale, rates of complete protection after 7 days of treatment	Primary: In the dolasetron arms, 57% had complete protection for the first 24 hours compared to the ondansetron arms which had 67% (*P*=0.013). Secondary: MNS was more pronounced on the dolasetron arm, but the difference did not reach statistical significance (*P*=0.051). MNS was significantly reduced with the addition of dexamethasone to either dolasetron or ondansetron (*P*=0.001). Complete protection rates over 7 days was not statistically different (*P*=0.459) between dolasetron (36%) and ondansetron (39%). The addition of dexamethasone to both dolasetron and ondansetron showed statistical improvement compared to no

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
followed by dexamethasone 8 mg PO and dolasetron 200 mg PO (arm 3) vs ondansetron 32 mg IV or 8 mg PO BID without dexamethasone followed by ondansetron 8 mg PO BID (arm 4) vs ondansetron 32 mg IV or 8 mg PO BID with dexamethasone 8 mg IV followed by ondansetron 8 mg PO BID and dexamethasone 8 mg PO (arm 5) vs ondansetron 32 mg IV or 8 mg PO BID with dexamethasone 8 mg IV followed by dexamethasone 8 mg PO (arm 6)				dexamethasone in protection from emesis over 7 days (P<0.001). Dizziness and vision abnormalities were more common in the ondansetron group compared to dolasetron (P<0.001). Diarrhea was more common in the dolasetron group (P=0.001).
del Giglio et al[39] Granisetron various IV and PO regimens vs ondansetron various IV and	MA, RCT CINV	14 studies which included 6,467 patients with >25 patients per arm Duration varied	Primary: Comparison of prophylaxis of acute or delayed nausea and vomiting in highly or moderately emetogenic	Primary: For all scenario comparisons (acute highly emetogenic, acute moderately emetogenic, delayed highly emetogenic, delayed moderately emetogenic), there were no statistical differences in efficacy between granisetron and ondansetron for rates of nausea or vomiting (P value not given). There was only one study that showed differences in toxicity

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
PO regimens			chemotherapy Secondary: Not reported	between granisetron and ondansetron. In this study, ondansetron was associated with more dizziness and abnormal vision than granisetron (*P* value not given). Secondary: Not reported
Jaing et al[40] Granisetron 0.5-1 mg PO vs ondansetron 0.15 mg/kg IV for 2 doses (1 hour prior to chemotherapy and 4 hours later) and then a single PO dose (8 hours after first dose)	OL, PRO, RCT, XO Patients 3-18 years old	N=33 24 hours	Primary: Number of emetic episodes within 24 hours of chemotherapy (complete efficacy was defined as no emetic episodes and no need for rescue medication) Secondary: Therapeutic success (defined as 0-2 emetic episodes), therapeutic failure (defined as 3 or more vomiting episodes)	Primary: Complete efficacy for granisetron and ondansetron was 60.6% and 45.5%, respectively (*P*=0.227). Secondary: Therapeutic success was 84.8% in the granisetron group and 87.9% in the ondansetron group (*P*=1.00). Therapeutic failure for granisetron and ondansetron was 15.2% and 12.1%, respectively (*P*=1.00).
Dempsey et al[41] Granisetron 10 µg/kg or 1 mg IV vs	RETRO Prophylactic efficacy in patients with breast cancer treated with cyclophosphamide	Data from 6 centers in the United States N=224 (n=68 for ondansetron 8 mg IV, n=76 for	Primary: Incidence of acute nausea or vomiting (occurring within 24 hours of completion of	Primary: Incidence of acute nausea was statistically greater with ondansetron 8 mg IV (50%) than ondansetron 32 mg IV (26%) or granisetron (25%; *P*<0.01 for both comparisons). Incidence of acute emesis was not different amongst the three groups (*P* value not given).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ondansetron 8 mg IV vs ondansetron 32 mg IV		ondansetron 32 mg IV, n=80 for granisetron 10 µg/kg or 1 mg IV) 72 hours	chemotherapy) Secondary: Incidence of delayed emesis (occurring 25-72 hours after chemotherapy), total control of CINV with or without dexamethasone	Secondary: Incidence of delayed nausea was 6% for ondansetron 8 mg IV, 9% for ondansetron 32 mg, and 9% for granisetron, which were not statistically different for any group (*P* value not given). Incidence of delayed emesis was not different amongst the three groups (*P* value not given). Total control of CINV without dexamethasone was 35% for ondansetron 8 mg, 33% for ondansetron 32 mg and 69% for granisetron (*P*=0.05 for granisetron vs ondansetron 8 mg). With the addition of dexamethasone, total control of CINV was not significantly different amongst the three groups (*P* value not given).
Lacerda et al[42] Granisetron 3 mg IV vs ondansetron 16 mg IV vs ondansetron 24 mg IV vs tropisetron 5 mg IV*	DB, PG, RCT Patients undergoing autologous or allogenic stem cell transplantation received daily IV doses of 5-HT_3 receptor antagonist during days of chemotherapy	N=100 Duration not specified	Primary: Complete response (no episodes of nausea or vomiting) Secondary: Major response (one episode), minimal response (2-4 episodes) and failure (more than 4 episodes of nausea or vomiting)	Primary: When comparing rates of complete response, there was a significant difference in the ondansetron 24 mg group (62.5%) compared to the granisetron group (27.8%; *P*=0.015) and tropisetron (16.7%; *P*=0.003). Complete response for ondansetron 16 mg was 31.3% but statistical difference from ondansetron 24 mg was not reported. There were no statistical differences in complete response rates between ondansetron 16 mg (31.3%), granisetron and tropisetron (*P* value not given). Secondary: There was a trend in the major response of ondansetron 24 mg versus granisetron (*P*=0.064). A significant difference was not observed with ondansetron 16 mg. No statistically significant differences were found between ondansetron 16 mg, granisetron or tropisetron (*P* values not given).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Walsh et al[43] Granisetron 10 µg/kg IV daily vs ondansetron 0.15 mg/kg IV every 8 hours	DB, PG, PRO, RCT Patients undergoing nontotal body irradiation-containing conditioning agents in hematopoietic stem cell transplant, in addition to dexamethasone and lorazepam	N=96 24 hours after completion of chemotherapy	Primary: Number of emetic episodes, nausea report until 24 hours after cessation of chemotherapy Secondary: Rates of complete response or major response	Primary: The median number of emetic episodes for the granisetron arm was 3 and for the ondansetron arm was 1 (*P*=0.228). Rating of nausea was equal between the groups on all days of measurement (*P*=0.563 to *P*=1.0). Secondary: On day 1, complete response for the granisetron group was 83% and major response was 13%. Complete response for the ondansetron group was 90% and major response was 6%. These differences were not statistically significant (*P*=1.00). There were no differences in adverse effects.
Orchard et al[44] Granisetron 7.5 µg/kg/dose (≥18 years) or 10 µg/kg/dose (<18 years) every 12 hours vs ondansetron 8 mg IV bolus then 0.015 mg/kg/hour (≥18 years) or 0.15 mg/kg bolus then 0.03 mg/kg/hour (<18 years)	DB, PRO, RCT Patients 2-65 years old undergoing hematopoietic cell transplantation, in addition to dexamethasone	N=187 9 days	Primary: Number of emetic episodes Secondary: Mean nausea score, complete control over emesis as defined by no emetic episodes and major control over emesis as defined by 1-2 emetic episodes in 24 hours	Primary: There were no statistical differences between granisetron (0.73) and ondansetron (0.86) for episodes of emesis (*P*=0.32). Secondary: There were no statistical differences in the mean nausea scores between granisetron (1.17) and ondansetron (1.29; *P*=0.32). When stratified by age: there were no statistical differences in the <18 year old group between granisetron (0.54) and ondansetron (0.87) in mean episodes of emesis per day (*P*=0.08) or for mean nausea score per day (granisetron 0.82, ondansetron 1.14; *P*=0.09). There were no statistical differences in the ≥18 year old group between granisetron (0.80) and ondansetron (0.86) in mean episodes of emesis per day (*P*=0.71) or for mean nausea score per day (granisetron 1.29, ondansetron 1.36; *P*=0.65). There were no differences between granisetron and ondansetron in number of days in which emesis control was complete (*P*=0.68) or major (*P*=0.68).
Kalaycio et al[45] Granisetron 0.5 mg IV bolus	DB, PRO, RCT Breast cancer	N=45 7 days	Primary: Incidence and severity of	Primary: Incidence of nausea was no different between ondansetron and granisetron (*P*=0.86).

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then 1 mg/24 hour continuous infusion vs ondansetron 8 mg IV bolus then 24 mg/24 hour continuous infusion	patients receiving cyclophosphamide, thiotepa, and carboplatin, in addition to dexamethasone		nausea Secondary: Incidence of emesis, number of patients experiencing no emetic episodes	Secondary: Incidence of emesis was not statistically different between granisetron and ondansetron (*P*=0.67). There was no statistical difference between the groups in regards to the number of patients experiencing no emetic episodes (granisetron 9.1% vs ondansetron 17.4%; *P*=0.67). There were no significant differences in adverse effects between granisetron and ondansetron.
Gralla et al[46] Ondansetron 32 mg IV vs palonosetron 0.25 mg IV vs palonsetron 0.75 mg IV	DB, PRO, RCT Patients receiving moderately emetogenic chemotherapy	N=570 5 days	Primary: Proportion of patients with no emetic episodes and no rescue medication (complete response) during the 24 hour period after chemotherapy (acute period) Secondary: Efficacy in treatment of delayed CINV (≤ 5 days post chemotherapy), overall tolerability	Primary: Complete response rates were significantly higher for palonosetron 0.25 mg (81.0%) than ondansetron (68.6%) during the acute period (*P*<0.01). Secondary: Complete response rates were significantly higher for palonosetron than ondansetron at 24-120 hours (74.1% vs 55.1%; *P*<0.01) and overall 0-120 hours (69.3% vs 50.3%; *P*<0.01). Complete response rates achieved with palonosetron 0.75 mg were numerically higher but not statistically different from ondansetron during all time intervals. Both treatments were well tolerated with adverse events reported in 16% of patients receiving palonosetron vs 13.9% of patients receiving ondansetron. Post hoc analysis revealed no differences in the duration of adverse events in patients treated with ondansetron vs palonosetron.
Aapro et al[47] Palonosetron 0.25 mg IV vs	RETRO post hoc analysis of studies by Eisenberg et al[37] and Gralla et al[46]	N=171 5 days	Primary: Complete response during the acute period (0-24 hours after	Primary: During the overall post chemotherapy period, complete response rate was significantly higher in the palonosetron group than in the ondansetron/dolasetron group (70.9% vs 51.2%; *P*=0.011).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ondansetron 32 mg IV or dolasetron 100 mg IV	Patients ≥65 years receiving moderately emetogenic chemotherapy		chemotherapy), delayed period (24-120 hours), and overall period (0-120 hours) with significance *P*≤ 0.025 Secondary: Not reported	The proportion of patients with complete response during the acute time period was not significantly different between the palonosetron and ondansetron/dolasetron groups (84.8% vs 74.4%; *P*>0.025). Complete response was significantly higher in the palonosetron group compared to the ondansetron/dolasetron group during the delayed period (72.2% vs 53.5%; *P*=0.016). Secondary: Not reported
Davidson et al[48] Ondansetron 8 mg OT BID for 3 days vs ondansetron 8 mg ODT BID for 3 days	DB, MC, PRO, RCT Patients receiving cyclophosphamide	N=427 3 days	Primary: Complete or major control of emesis on their worst of days 1 through 3 Secondary: Not reported	Primary: Complete or major control of emesis was achieved by 80% of OT patients and 78% of ODT patients (90% CI, -8.6% to 4.4% with ±15% limit for equivalence). Complete control of emesis for days 1 through 3 was not significantly different between the treatment groups with 63% of OT and 64% of ODT patients. There was no significant difference in overall incidence of adverse effects between the 2 formulations. The most common adverse effects reported and those most frequently assessed as drug-related were headache (OT 11% vs ODT 9%) and constipation (both 10%). Secondary: Not reported
Radiation-Induced Nausea and Vomiting (RINV)				
Spitzer et al[49] Granisetron 2 mg PO vs ondansetron 8 mg PO	DB, PG, PRO, RCT Patients ≥18 years diagnosed with malignant disease or aplastic anemia receiving 11	N=34 4 days	Primary: Number of patients who had 0 emetic episodes over 4 days	Primary: Significantly more patients given granisetron (33.3%) and ondansetron (26.7%) experienced no episodes of emesis than the historical control (0%; *P*<0.01 for both granisetron and ondansetron compared to historical control). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs historical control	fractions of radiation over the course of 4 days		Secondary: Percent of patients with 0 emetic episodes and no rescue medication over 24 hours and 4 days	During the first 24 hours, significantly more patients receiving granisetron (61.1%) and ondansetron (46.7%) had no emetic episodes than the historical control group (6.7%; *P*<0.01). Within the first 4 days, fewer patients in the granisetron (27.8%) and ondansetron groups (26.7%) had 0 emetic episodes and needed no rescue medication compared to historical controls (0%; *P*<0.01).
Postoperative Nausea and Vomiting (PONV)				
Olutoye et al[50] Dolasetron 45 µg/kg IV vs dolasetron 175 µg/kg IV vs dolasetron 350 µg/kg IV vs dolasetron 700 µg/kg IV vs ondansetron 100 µg/kg IV	DB, PG, PRO, RCT Patients 2-12 years old receiving day surgery	N=204 Duration not specified	Primary: Complete response (no postoperative emetic symptoms) Secondary: Not reported	Primary: There were no significant differences in complete response between ondansetron 100 µg/kg, dolasetron 700 µg/kg and dolasetron 350 µg/kg. Ondansetron, dolasetron 700 µg/kg and dolasetron 350 µg/kg were all statistically better than dolasetron 175 µg/kg and dolasetron 45 µg/kg (*P*<0.05). Secondary: Not reported
Meyer et al[51] Dolasetron 12.5 mg IV vs ondansetron 4 mg IV	DB, PRO, RCT Patients undergoing day surgery	N=92 Duration not specified	Primary: Need for antiemetic rescue medication Secondary: Evaluation of nausea and	Primary: The need for rescue antiemetic in the dolasetron group was 40% compared to the ondansetron group which was 70% (*P*<0.004). Secondary: There was no significant difference between the two groups in regards to the number of patients who actually vomited (*P*=0.34).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			vomiting within 24 hours of surgery, overall time until discharge-ready in day surgery, overall time spent in PACU	The overall time until discharge-ready in day surgery was 131 minutes for dolasetron and 158 minutes for ondansetron (*P*=0.17). The overall time spent in the PACU was similar between groups (*P*=0.99).
Walker[52] Dolasetron 12.5 mg IV vs ondansetron 4 mg IV	RETRO Medical charts of patients who underwent total abdominal hysterectomy or laparoscopic cholecystectomy	N=59 24 hours	Primary: Number of recorded episodes of PONV in 24 hours after surgery, time to occurrence of PONV Secondary: Not reported	Primary: PONV occurred in 44% patients receiving dolasetron and 53% patients receiving ondansetron. Four patients (36%) receiving dolasetron experienced PONV in the first 2 hours after surgery, compared with 7 patients (39%) receiving ondansetron. Differences in primary end points did not reach statistical significance (*P* value not reported). Secondary: Not reported
Karamanlioglu et al[53] Dolasetron 1.8 mg/kg PO vs ondansetron 0.15 mg/kg PO vs placebo Medications were given 1 hour before induction of surgery.	DB, PRO, RCT Children undergoing elective strabismus surgery, middle ear surgery, adenotonsillectomy or orchiopexy	N=150 Duration not specified	Primary: Nausea and vomiting rates, total nausea and vomiting score Secondary: Not reported	Primary: Over the 0-24 hour period, both dolasetron and ondansetron were significantly better than placebo in nausea (16% vs 26% vs 40%), vomiting (8% vs 16% vs 30%) and total nausea and vomiting scores (32% vs 48% vs 78%; *P*<0.05 compared to placebo) There were no significant differences between dolasetron and ondansetron (no *P* values reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
White et al[54] Granisetron 1 mg PO one hour before surgery vs ondansetron 4 mg IV at the end of surgery	DB, MC, PRO, RCT Patients undergoing laparoscopic surgery	N=220 24 hours post surgery	Primary: Postoperative episodes of emesis, patient report of nausea, need for rescue antiemetic medication Secondary: Not reported	Primary: PONV <4 hours post surgery: nausea was reported in 47% and 43% of ondansetron and granisetron patients, respectively. Vomiting was noted in 22% of both ondansetron and granisetron patients. Rescue antiemetics were used in 34% and 39% of ondansetron and granisetron patients, respectively. PONV 4-24 hours post surgery: nausea was reported in 46% and 38% of ondansetron and granisetron patients, respectively. Vomiting was noted in 23% and 13% of ondansetron and granisetron patients, respectively. Rescue antiemetics were used in 25% and 24% of ondansetron and granisetron patients, respectively. None of these comparisons were significantly different from each other (*P* values not given). Secondary: Not reported
Gan et al[55] Granisetron 0.1 mg IV and dexamethasone 8 mg IV vs ondansetron 4 mg IV and dexamethasone 8 mg IV	DB, MC, PG, PRO, RCT Patients undergoing abdominal hysterectomy, medications given 15 minutes prior to end of surgery	N=176 24 hours post surgery	Primary: Proportion of patients with no vomiting during 0-2 hours post surgery Secondary: Proportion of patients with no vomiting during 0-6 hours and overall 0-24 hours post surgery	Primary: From 0-2 hours post surgery, the granisetron group had no emesis in 94% of patients and the ondansetron group had no emesis in 97% of patients. The difference was not statistically significant (95% CI, -8.5 to 3.8). Secondary: From 0-6 hours post surgery, the granisetron group had no emesis in 87% of patients and the ondansetron group had no emesis in 93% of patients. This difference was not statistically significant (95% CI, -14.6 to 2.8). From 0-24 hours post surgery, the granisetron and ondansetron groups had no emesis in 83% and 87% of its patients, respectively. The difference was not statistically significant (95% CI, -14.4 to 6.9).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Gan et al[56] Ondansetron ODT 8 mg before discharge and 12 hours later vs placebo ODT	DB, PC, PRO, RCT Patients undergoing outpatient gynecological laparoscopy	N=60 24 hours post surgery	Primary: Incidence of PONV, severity of nausea, rescue antiemetic, side effects, satisfaction PONV manage-ment assessed at 2 and 24 hours post surgery Secondary: Not reported	Primary: Ondansetron ODT patients had significantly less post discharge emesis (3% vs 23%), and less severe nausea after discharge compared to placebo patients (P<0.05). The ondansetron ODT group was more satisfied with PONV control than placebo (90% vs 63%; P<0.05). Ondansetron ODT was less acceptable to patients although they would use it again (P<0.01). Patients rated the taste of ondansetron ODT less favorably than the placebo ODT. Secondary: Not reported
Loewen et al[57] 5-HT_3 antagonists (dosages and routes were not specified) vs traditional agents (metoclopramide, perphenazine, prochlorperazine, cyclizine and droperidol)	MA Review of randomized, double-blind, controlled clinical trials published in English and in MEDLINE or EMBASE from 1966-October 1999	41 trials met criteria 5-HT_3 antagonists N=2,855 and traditional agents N=3,783	Primary: Postoperative nausea and vomiting that occurred within 48 hours after surgery Secondary: 5-HT_3 receptor antagonists compared to traditional antiemetics for rates of vomiting	Primary: 5-HT_3 receptor antagonists showed a 46% reduction in the odds of PONV (OR, 0.54; 95% CI, 0.42 to 0.71; P<0.001). 5-HT_3 receptor antagonists showed a 39% reduction in PONV over droperidol (OR, 0.61; 95% CI, 0.42 to 0.89; P<0.001). 5-HT_3 receptor antagonists showed a 56% reduction in PONV over metoclopramide (OR, 0.44; 95% CI, 0.31 to 0.62; P<0.001). Secondary: 5-HT_3 receptor antagonists showed a 38% reduction in vomiting compared to traditional antiemetics (OR, 0.62; 95% CI, 0.48 to 0.81; P<0.001). 5-HT_3 antagonists showed a beneficial effect over droperidol in rate of vomiting (OR, 0.56; 95% CI, 0.41 to 0.76; P<0.001). 5-HT_3 antagonists showed a beneficial effect over metoclopramide in rate of vomiting (OR, 0.50; 95% CI, 0.32 to 0.77; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Sedation was more common in the traditional group (11.9%) compared to 5-HT_3 receptor antagonists (5.6%; OR, 0.7; 95% CI, 0.32 to 0.64; *P*<0.001). Headache was more common in the 5-HT_3 receptor antagonist group (17.0%) than in the traditional antiemetic group (13.0%; OR, 1.65; 95% CI, 1.35 to 2.02; *P*<0.001).
Eberhart, et al[58] Dolasetron 12.5 mg IV vs droperidol 10 µg/kg IV vs dolasetron 12.5 mg and droperidol 10 µg/kg IV vs placebo	DB, PG, RCT Patients undergoing vitreoretinal surgery received study medication 5-10 minutes before the end of surgery	N=304 Duration not specified	Primary: Mean PONV score (0-3, with 0 being no nausea or vomiting) with a significance level of *P*=0.01 Secondary: Complete prevention of PONV	Primary: Droperidol was statistically better than placebo (*P*<0.0001) in reduction of mean PONV score. Dolasetron was numerically better but not statistically better than placebo (*P*=0.017). Combination therapy was statistically better than placebo (*P*<0.0001) in reduction of mean PONV score. Droperidol and dolasetron were not statistically different from each other (*P*=0.096), although droperidol was numerically better in the reduction of mean PONV score. Secondary: Droperidol was statistically better than placebo (*P*<0.0006) in complete prevention of PONV. Dolasetron was numerically better but not statistically better than placebo (*P*=0.038). Combination therapy was statistically better than placebo (*P*<0.0001) in complete prevention of PONV. Droperidol and dolasetron were not statistically different from each other (*P*=0.17) although droperidol was numerically better in complete prevention of PONV.
Hamid et al[59] Dimenhydrinate 0.5 mg/kg vs ondansetron 0.1 mg/kg IV	DB, PC, PRO, RCT Children 2-10 years of age scheduled for adenotonsillectomy	N=47 24 hours	Primary: Incidence of retching and vomiting observed during the first 24 hours post surgery	Primary: The incidence of POV during the first 24 hours after surgery in the ondansetron group (42%) was significantly less than in the dimenhydrinate (79%; *P*<0.02) and placebo (82%; *P*<0.01) groups. The number of episodes of POV in the first 24 hours differed significantly between the ondansetron and placebo groups only.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo All were given at induction of anesthesia.			Secondary: Not reported	The number of children whose discharges from hospital were delayed secondary to POV in the ondansetron group (0 of 25) was significantly less than in the placebo group (4 of 22; *P*<0.04) Secondary: Not reported
Kothari et al[60] Dimenhydrinate 50 mg IV vs ondansetron 4 mg IV All medications were administered before induction of anesthesia.	DB, PRO, RCT Consecutive patients undergoing laparoscopic cholecystectomy	N=128 24 hours after discharge	Primary: Frequency of PONV, need for rescue antiemetics, need for overnight hospitalization secondary to persistent nausea and vomiting, frequency of PONV 24 hours after discharge Secondary: Not reported	Primary: Need for rescue medication occurred in 34% of ondansetron group and 29% of dimenhydrinate group (*P*=0.376). Postoperative vomiting occurred in 6% of ondansetron group and 12% of dimenhydrinate group (*P*=0.228). Postoperative nausea and vomiting occurred in 42% of ondansetron group and 34% of dimenhydrinate group (*P*=0.422). One patient in the ondansetron group and 2 patients in the dimenhydrinate group required overnight hospitalization for persistent nausea and vomiting (*P*=not significant). Rates of postoperative nausea and vomiting 24 hours after discharge were similar between the ondansetron and dimenhydrinate groups (10% and 14%; *P*=0.397 and 2% and 5%; *P*=0.375, respectively). Secondary: Not reported
McCall et al[61] Dimenhydrinate 0.5 mg/kg vs ondansetron 0.1 mg/kg	DB, PC, PRO, RCT Patients with a mean age of 11.8 years undergoing reconstructive burn surgery with general anesthesia	N=100 8 hours	Primary: Incidence of PONV, POV Secondary: Not reported	Primary: Statistically significant reductions in the incidence of PONV in the patients who received ondansetron or dimenhydrinate were found, as compared with the results of patients who received placebo. POV was reduced from 61% in the placebo group to 29% and 40% in the ondansetron and dimenhydrinate groups, respectively, and PONV was similarly reduced from 69% to 47% and 40%,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo Study drugs were given at the end of surgery and again 4 hours later.				respectively. The differences between ondansetron and dimenhydrinate were not statistically significant. Secondary: Not reported
Van den Berg[62] Prochlorperazine 0.2 mg/kg IM vs prochlorperazine 0.2 mg/kg IV vs ondansetron 0.06 mg/kg IV vs placebo All were given with induction of anesthesia.	DB, PRO, RCT Patients from 9-61 years of age received standardized general anesthesia for tympanoplasty	N=148 24 hours	Primary: Incidence of retching and vomiting in the PACU during first 24 hours post surgery Secondary: Postoperative headache	Primary: Nausea alone during the first 24-hour postoperative period was infrequent in each treatment group with a similar incidence (3%-8%). The incidence of vomiting alone (without accompanied nausea) during this time was also similar between groups (11%-24%). The incidence of vomiting or retching immediately after extubation or during recovery occurred in 16% of placebo patients, 5% of patients in the IM prochlorperazine group, and 8% in the prochlorperazine and ondansetron IV groups, but the differences between groups was not significant (P>0.05 for all groups). The incidence of nausea accompanied by vomiting occurred in 53% of patients in the placebo group, 16% in those given prochlorperazine IM (P<0.0005), 19% in those given ondansetron IV (P<0.0005) and 30% in those given prochlorperazine IV (P<0.05). The study was not powered to detect a difference between active treatment groups. The percent of patients who experienced no nausea or vomiting was 27% for placebo, 57% for prochlorperazine IM, 43% for prochlorperazine IV, and 62% for ondansetron IV. Only the prochlorperazine IM and ondansetron IV groups achieved significance compared to placebo (P<0.01 and P=0.005, respectively). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Incidence of headache reported in the first 24 hours after surgery (placebo 56%, prochlorperazine IM 41%, prochlorperazine IV 43% and ondansetron IV 49%) was similar in the four groups.
Chen et al[63] Prochlorperazine maleate 10 mg IM vs ondansetron 4 mg IV All were administered at end of surgical procedure.	DB, RCT Patients greater than 17 years old undergoing elective, primary or revisionary total hip or total knee replacement procedures	N=78 48 hours postoperatively	Primary: Incidence and severity of PONV Secondary: Number of rescue antiemetic doses required, number of physical therapy cancellations because of PONV, length of hospital stay	Primary: The incidence of nausea was significantly greater in the ondansetron group compared with the prochlorperazine group (*P*=0.02), as was the severity of nausea (*P*=0.04). The incidence (*P*=0.13) and severity (*P*=0.51) of vomiting were similar between the two groups. Secondary: The need for rescue antiemetic therapy was greater in the ondansetron group compared to the prochlorperazine group, but the difference was not statistically significant (*P*=0.08). The mean number of rescue antiemetic doses required was 2.1 in the ondansetron group and 1.7 in the prochlorperazine group, but the difference did not reach statistical difference (*P*=0.50).
Erhan et al[64] granisetron 3 mg IV vs ondansetron 4 mg IV vs dexamethasone 8 mg IV vs placebo	DB, PC, PRO, RCT Patients between the ages of 21-75 years with an ASA physical class of I-II, scheduled for laparoscopic cholecystectomy with general anesthesia	N=80 Monitored over 24 hour time period	Primary: Complete response (no postoperative emetic symptoms) Secondary: Not reported	Primary: The occurrence of nausea and vomiting for the different groups were: ondansetron (35%), granisetron (30%), dexamethasone (25%) and placebo (75%). All *P* values were less then 0.05 for comparisons to placebo. Secondary: Not reported
Kovac et al[65]	DB, MC, PC, PRO, RCT	N=544	Primary: Complete	Primary: Compared to placebo (36%), complete response was 46% for

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
palonosetron 0.025 mg IV vs palonsetron 0.050 mg IV vs palonsetron 0.075 mg IV vs placebo	Female patients with an ASA status I-III, greater than 18 years old, scheduled to undergo elective inpatient gynecological or breast surgery that was expected to last a minimum of 1 hour and were scheduled to be hospitalized for at least 72 hours after surgery	Monitored over 72 hour time period	response (no postoperative emetic symptoms) over 0-24 hours and 24-72 hours Secondary: Time to treatment failure, use of rescue therapy, emetic episodes, nausea and safety	palonosetron 0.025 mg (*P*=0.069), 47% for palonosetron 0.05 mg (*P*=0.069) and 56% for palonsetron 0.075 mg (*P*=0.001) when evaluated at the 0-24 hour time interval after surgery. Complete response for placebo and palonosetron 0.075 mg were 52% and 70% for the 24-74 hour time interval (*P*=0.002). Complete response rates for palonosetron 0.025 mg and 0.050 mg were not statistically different than placebo. Secondary: A significantly longer time to treatment failure was observed in the palonosetron 0.075 mg group vs placebo (*P*=0.004). No significant time difference was seen between placebo and palonosetron 0.025 mg group (*P*=0.112) and palonosetron 0.05 mg group (*P*=0.060). During the 0-72 hour study period 62/136 (46%) placebo patients compared to 36/135 (27%) palonosetron 0.075 mg patients required rescue medication (*P*<0.001). During the 0-24 hour time block 82/136 (60%) placebo patients compared to 54/136 (46%) palonsetron 0.075 mg patients experience an emetic episode (*P*<0.001). During the 24-72 hour time block there was no significant difference between the placebo (10%) and palonosetron 0.075 mg groups (4%; *P*=0.061). During the 0-24 hour time block significantly fewer patient treated with palonosetron 0.075 mg (50%) compared to placebo (71%) experienced nausea (*P*<0.001). All doses of palonosetron were well tolerated in this study. Percentages of severe adverse events were 5% in the placebo group, 4% in the palonosetron 0.075 mg group, and 7% in both the palonosetron 0.025 mg and 0.05 mg groups. Not all values were reported in secondary end points.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Candiotti et al[66] Palonosetron 0.025 mg IV vs palonosetron 0.05 mg IV vs palonsetron 0.075 mg IV vs placebo	DB, MC, PC, PRO, RCT Patients at least 18 years old with an ASA physical status of I-III and scheduled to undergo elective laparoscopic abdominal or gynecological surgery and had to have at least two of the following risk factors: female gender, history of PONV and/or motion sickness, or nonsmoking status	N=546 Monitored over 72 hour time period	Primary: Complete response (no postoperative emetic symptoms) over 0-24 hours and 24-72 hours Secondary: Emetic episodes, nausea, interference of PONV with patient functions and safety	Primary: Complete response at 0-24 hours was 26% in the placebo group compared with 33% of the palonsetron 0.025 mg group (*P*=0.187), 39% in the palonosetron 0.050 mg group (*P*=0.017) and 43% in the palonosetron 0.075 mg group (*P*=0.004). Complete response at 24-72 hours was 41% in the placebo group compared to 44% in the palonsetron 0.025 mg group (*P*=0.638), 47% in the palonosetron 0.050 mg group (*P*=0.249) and 49% in the palonosetron 0.075 mg group (*P*=0.188). Secondary: Emetic episodes at 0-72 hours were 33% in the palonosetron 0.075 mg group compared to 44% in the placebo group(*P*=0.075). During the 0-24 hour time period more patients receiving palonosetron 0.075 mg did not experience nausea (*P*=0.033) or experienced less intense nausea (*P*=0.0504) compared to placebo. Total Osoba questionnaire scores (evaluating interference of PONV with patient function) were better with palonosetron 0.075 mg than placebo (*P*=0.004). Adverse events were reported in 7% of patients in the palonosetron 0.075 mg group and 10% in placebo group (*P* values not reported). Only values of palonosetron 0.075 mg group were reported for the secondary end points.

*Agent not available in the United States
Drug regimen abbreviations: BID=twice daily, IM=intramuscular, IV=intravenous, ODT=orally disintegrating tablet, OT=oral tablet, PO=by mouth
Study abbreviations: CI=confidence interval, DB=double-blind, MA=meta-analysis, MC=multicenter, OL=open-labeled, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, XO=crossover
Miscellaneous abbreviations: ASA=American Society of Anesthesiologist, CINV=chemotherapy-induced nausea and vomiting, MNS=mean nausea score, PACU=post anesthesia care unit, PONV=postoperative nausea and vomiting, POV=postoperative vomiting, RINV=radiation-induced nausea and vomiting

Special Populations

Table 5. Special Populations [27-30]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Dolasetron	No dose adjustment required for elderly or children. Approved for use in children 2 to 16 years of age. Not studied in patients under 2 years of age.	Renal dose adjustment not required.	Hepatic dose adjustment not required.	B	Not known.
Granisetron	No dose adjustment required for elderly or children. Approved for use in children 2 to 16 years of age. Not studied in patients under 2 years of age.	Renal dose adjustment not required.	Hepatic dose adjustment not required.	B	Not known.
Ondansetron	No geriatric dosage adjustment required. Children over 12 no dosage adjustment required. Children ages 4-11, half adult dose. Not studied in patients under the age of 4.	Renal dose adjustment not required.	In severe hepatic impairment (Child-Pugh score of 10 or greater), do not exceed 8 mg per day.	B	Not known.
Palonosetron	No geriatric dosage adjustment required. Not studied in patients under 18 years of age.	Renal dose adjustment not required.	Hepatic dose adjustment not required.	B	Not known.

Adverse Drug Events

The 5-HT_3 receptor antagonists are generally very well tolerated. There is a warning and general precaution for dolasetron regarding the risk of arrhythmias. This risk has not caused any evidence-based or expert consensus guideline to advise against the use of dolasetron. Ondansetron and palonosetron have QTc prolongation as a general precaution but observed electrocardiogram (ECG) changes have been less than 1%.[27-30] The most common adverse reactions reported with the single entity 5-HT_3 antagonists are included in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Single Entity 5-HT$_3$ Receptor Antagonists[27-36]

Adverse Event(s)	Dolasetron	Granisetron	Ondansetron	Palonosetron
Cardiovascular				
Bradycardia	4-5.1	4.5	6	1-4
Hypertension	2.9	2-2.6	2.5	<1
Hypotension	5.3	3.4	3-5	1
Tachycardia	2.2-3	-	-	1
Central Nervous System				
Anxiety	-	3.4	6	1
Chills/shivering	2.0	5	7	-
Dizziness	2.2-5.5	4.1	4-7	1
Drowsiness	2.4	-	20	-
Headache	9.4-24.3	8.6	9-27	3-9
Insomnia	-	4.9	-	<1
Malaise/fatigue	3.4	-	9-13	<1
Paresthesia	-	-	2	-
Somnolence	-	4	-	<1
Dermatological				
Pruritis	3.1	-	2-5	-
Skin rashes	-	1	-	<1
Endocrine and Metabolic				
Increased AST and ALT	3.6	5.6	3.4	<1
Gastrointestinal				
Abdominal pain	3.2	6	3	<1
Constipation	-	3-9.4	6-9	2-5
Diarrhea	12.4	3.4-4	4-7	1
Dyspepsia	2.2-3	3.0	-	<1
Flatulence	-	3	-	<1
Xerostomia	-	-	2	<1
Genitourinary				
Oliguria	2.6	2.2	-	-
Urinary retention	2	-	3-5	<1
Urinary tract infection	-	2.6	-	-
Musculoskeletal				
Asthenia	-	5	-	-
Other				
Anemia	-	9.4	-	-
Cold sensation	-	-	2	-
Coughing	-	2.2	-	-
Fever/pyrexia	3-4.3	7.9-8.6	2-8	<1
Gynecological disorder	-	-	6-7	-
Hypoxia	-	-	9	-
Injection site reaction	-	-	4	-
Leukocytosis	-	3.7	-	-
Pain	2.4	10.1	2	-
Taste disorder	-	2	-	-
Weakness	-	-	2	1
Wound problems	-	-	11-28	-

ALT=alanine aminotransferase, AST=aspartate aminotransferase
- Event not reported or incidence <1%.

Drug Interactions

Table 7. Drug Interactions[36]

Generic Name	Interacting Medication or Disease	Potential Result
Dolasetron	Ziprasidone	A possible additive or synergistic prolongation of the QT interval may occur.
Dolasetron, ondansetron	Rifamycins (rifabutin, rifampin, rifapentine)	Rifamycins may decrease the half-life and increase the clearance of ondansetron and dolasetron through induction of hepatic metabolism.

Dosage and Administration

Table 8. Dosing and Administration[27-30]

Generic Name	Adult Dose	Pediatric Dose	Availability
Dolasetron	CINV: 100 mg PO, day 1 or 1.8 mg/kg or 100 mg IV, day 1 100 mg PO DAILY, days 2-4 or 1.8 mg/kg or 100 mg IV DAILY, days 2-4 PONV: 100 mg PO or 12.5 mg IV	Age 2-16 years; CINV: 1.8 mg/kg up to 100 mg PO, day 1 or 1.8 mg/kg IV (maximum 100 mg) PONV: 1.2 mg/kg up to 100 mg PO or 0.35 mg/kg IV	Ampule for injection: 12.5 mg/0.625 mL Injection device: 12.5 mg/0.625 mL Tablet: 50 mg 100 mg Vial for injection: 12.5 mg/0.625 mL 100 mg/5 mL 500 mg/25 mL
Granisetron	CINV: 2 mg PO, day 1 or 0.01 mg/kg IV (maximum 1 mg), day 1 1-2 mg PO DAILY, days 2-4 or 0.01 mg/kg IV DAILY (maximum 1 mg), days 2-4 PONV: 1 mg IV RINV: 2 mg PO DAILY	Age 2-16 years; CINV: 2 mg PO or 0.01 mg/kg IV (maximum 1 mg) PONV: Safety and efficacy in children have not been established. RINV: Safety and efficacy in children have not been established.	Solution: 6 mg/30 mL Tablet: 1 mg Vial for injection: 1 mg/1 mL 4 mg/4 mL 0.1 mg/1 mL
Ondansetron	CINV: 8 mg TID PO, day 1 or 24 mg PO, day 1 or 32 mg IV, day 1 8 mg PO BID/16 mg PO	CINV: Ages 4-11 years: 4 mg TID PO or Ages 6 months-18 years: 0.15 mg/kg IV TID	ODT: 4 mg 8 mg Solution: 4 mg/5 mL

Generic Name	Adult Dose	Pediatric Dose	Availability
	DAILY, days 2-4 or 8 mg IV DAILY (maximum 32 mg), days 2-4 PONV: 16 mg PO or 4 mg IV RINV: 8 mg PO TID	PONV: Age 1 month to 12 years 0.1 mg/kg IV RINV: Safety and efficacy in children have not been established.	Tablet: 4 mg 8 mg 24 mg Vial for injection: 4 mg/2 mL 40 mg/20 mL 32 mg/50 mL
Palonosetron	CINV: 0.25 mg IV, day 1 PONV: 0.075 mg IV	CINV: Safety and efficacy in children have not been established. PONV: Safety and efficacy in children have not been established.	Vial for injection: 0.25 mg/5 mL 0.075mg/1.5 mL

BID=twice daily, CINV=chemotherapy-induced nausea and vomiting, IV=intravenous, ODT=orally disintegrating tablet, PO=oral, PONV=postoperative nausea and vomiting, RINV=radiation-induced nausea and vomiting, TID=three times daily

Other Key Facts

Clinical Guidelines

Table 10. Clinical Guidelines Using the Single Entity 5-HT$_3$ Receptor Antagonists

Clinical Guideline	Recommendations
American Society of Clinical Oncology (ASCO): **Guideline for Antiemetics in Oncology: Update (2006)**[20]	• For prophylaxis of acute onset in high emetic risk chemotherapy: any 5-HT$_3$ receptor antagonist, dexamethasone, and aprepitant are recommended. • For prophylaxis of acute onset in moderate emetic risk chemotherapy: any 5-HT$_3$ receptor antagonist, dexamethasone, and the addition of aprepitant if the patient is taking anthracycline and cyclophosphamide. • For prophylaxis of acute onset in low risk emetic chemotherapy: dexamethasone 8 mg is recommended. • Emesis in pediatric patients: any 5-HT$_3$ receptor antagonist with a corticosteroid is recommended. • For prophylaxis of radiation-induced emesis: any 5-HT$_3$ receptor antagonist with or without a corticosteroid is recommended.
National Comprehensive Cancer Network (NCCN): **Practice Guidelines in Oncology: Antiemesis (2008)**[21]	• For high emetic risk chemotherapy, the combination of aprepitant, dexamethasone and any 5-HT$_3$ receptor antagonist, with or without lorazepam is recommended. • For moderate emetic risk chemotherapy, the combination of aprepitant, dexamethasone, and any 5-HT$_3$ receptor antagonist, with or without lorazepam should be used for day 1 treatment. For days 2-3, aprepitant +/- dexamethasone with or without lorazepam, OR dexamethasone, OR ondansetron, granisetron or dolasetron; for breakthrough emesis, give an additional agent from another class. • For low and minimal emetic risk chemotherapy, dexamethasone OR

Clinical Guideline	Recommendations
	prochlorperazine OR metoclopramide +/- diphenhydramine, with or without lorazepam. • For upper abdomen radiation therapy, use ondansetron or granisetron or dexamethasone. • For total body radiation, use ondansetron or granisetron, with or without dexamethasone. • 5-HT_3 receptor antagonists are not recommended for anticipatory nausea and vomiting.
Multinational Association of Supportive Care in Cancer (MASCC): **Prevention of Chemotherapy- and Radiotherapy-Induced Emesis: The Results of the 2004 Perugia International Antiemetic Consensus Conference**[22]	• For the prophylactic treatment of acute emesis in highly emetogenic chemotherapy, a 3-drug regimen is recommended, including any 5-HT_3 receptor antagonist, dexamethasone, and aprepitant. • For the prophylactic treatment of acute emesis in moderately emetogenic chemotherapy, a 3-drug regimen is recommended if the regimen contains anthracycline plus cyclophosphamide. This regimen consists of any 5-HT_3 receptor antagonist, dexamethasone, and aprepitant. • For the prophylactic treatment of acute emesis in moderately emetogenic chemotherapy, not containing anthracycline plus cyclophosphamide, a 2-drug regimen that consists of any 5-HT_3 receptor antagonist and dexamethasone is recommended. • For the prophylactic treatment of delayed emesis in moderately emetogenic chemotherapy, containing anthracycline plus cyclophosphamide, that is being treated with a 5-HT_3 receptor antagonist and dexamethasone to prevent acute nausea and vomiting, aprepitant or dexamethasone is suggested to prevent delayed emesis. • For the prophylactic treatment of delayed emesis in moderately emetogenic chemotherapy, who did not receive aprepitant as part of the treatment for acute emesis, oral dexamethasone is the preferred treatment • For prophylactic treatment of acute emesis in low risk emetogenic chemotherapy, a single agent, such as a low dose of a corticosteroid, is recommended. • For the prophylactic treatment of nausea and vomiting in patients receiving highly emetic radiation therapy, a 5-HT_3 receptor antagonist plus dexamethasone is recommended. • For the prophylactic treatment of nausea and vomiting in patients receiving moderately emetic radiation therapy, a 5-HT_3 antagonist is recommended. • For the patient receiving radiation therapy of low emetic risk, rescue therapy with a dopamine antagonist or a 5-HT_3 receptor antagonist is recommended.
American Gastroenterological Association Institute: **American Gastroenterological Association Medical Position Statement: Nausea and Vomiting (2001)**[23]	• 5-HT_3 receptor antagonists are recommended for the first-line treatment of chemotherapy-related and postoperative nausea and vomiting.
Society of Obstetricians and Gynaecologists of Canada Clinical	• Ondansetron may be safe to use during the first trimester of pregnancy. Due to its limited effectiveness data, it should not be used as a first-line agent.

Clinical Guideline	Recommendations
Practice Guidelines: **The Management of Nausea and Vomiting of Pregnancy (2002)**[24]	
The International Anesthesia Research Society: **Consensus Guidelines for Managing PONV (2003)**[25]	• 5-HT_3 receptor antagonists are recommended for prophylaxis of postoperative nausea and vomiting (PONV) and studies have shown no difference in the safety and efficacy profile of any of the agents in this class. • Small-doses of 5-HT_3 receptor antagonists are recommended for the treatment of PONV in patients who did not receive prophylactic treatment. • Small-doses of 5-HT_3 receptor antagonists are recommended in patients when prophylaxis with dexamethasone fails to prevent PONV, but when a 5-HT_3 receptor antagonist fails as prophylaxis, another 5-HT_3 receptor antagonist should not be used as rescue therapy within the first 6 hours after surgery. • If PONV occurs more than 6 hours after surgery, repeat dosing of 5-HT_3 receptor antagonists may be considered.
American College of Obstetricians and Gynecologists (ACOG): **ACOG Practice Bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists. Nausea and Vomiting of Pregnancy (2004)**[26]	• Patients who are taking a multivitamin at the time of conception may experience less nausea and vomiting during pregnancy. • First-line therapy is vitamin B6 (pyridoxine) with or without doxylamine (this combination product is no longer available in the United States, but the individual components are available). • Pharmacological therapy that is considered safe and efficacious in pregnancy includes antihistamines, phenothiazines, and benzamides (trimethobenzamide). • Severe nausea and vomiting of pregnancy or hyperemesis gravidarum may be treated with methylprednisolone as a last resort. • The use of 5-HT_3 receptor antagonists in pregnancy is controversial, though ondansetron may be used as an alternative to methylprednisolone. In practice the use of 5-HT_3 receptor antagonists in pregnancy appears to by increasing.

Conclusions

Nausea and vomiting are significant problems particularly in the treatment of cancer and following surgery. Physiologic pathways involved in the treatment of nausea and vomiting primarily involve dopamine and serotonin (5-HT). Other receptors, which have a smaller role, include muscarinic, opiate, histamine-1, cannabinoid and neurokinin-1 receptors.[1-4]

Treatment of chemotherapy- or radiation-induced nausea and vomiting generally involves the use of multiple agents that affect different receptor types, such as a dopamine antagonist, a corticosteroid and a 5-HT_3 receptor antagonist. Choice of agents generally depends upon the relative emetogenic potential of the regimen. When choosing among a class of agents, guidelines have suggested that all 5-HT_3 receptor antagonists can be appropriately dosed to provide equivalent efficacy.[13-22] If one 5-HT_3 receptor antagonist is ineffective, switching to another 5-HT_3 receptor antagonist may be appropriate.[32, 67] If breakthrough emesis or nausea occurs, adding an agent with a different mechanism of action (cannabinoid receptor agonist, cholinergic antagonist, or antihistamine) may be appropriate.[1,4,6,14,17]

The 5-HT_3 receptor antagonists are considered part of the standard of care in the management of chemotherapy-induced nausea and vomiting (CINV) due to chemotherapeutic agents with moderate-to-high emetic risk. All of these agents have been shown to be equally effective in preventing acute CINV and the treatment guidelines do not distinguish one agent from another. Single dose therapy with palonosetron was reported to be more effective than other medications in the class at preventing delayed

emesis.[37] The manufacturer's product labeling also reports that single dose intravenous administration of palonosetron 0.25 mg was more effective than ondansetron 32 mg for preventing delayed emesis.[27] Palonosetron has a longer half-life that the other 5-HT_3 receptor antagonists. The treatment guidelines do not give preference to palonosetron over repeat doses of shorter acting 5-HT_3 receptor antagonists. Granisetron and ondansetron are indicated for the treatment of radiation-induced nausea and vomiting (RINV) and have been shown to be equally effective.[49] All of these agents are indicated for the treatment of postoperative nausea and vomiting (PONV).[27-30] Clinical studies have shown these agents have comparable efficacy and the national guidelines do not distinguish one agent versus another.[25, 49-54] Several studies have demonstrated that dimenhydrinate and prochlorperazine were as efficacious as the 5-HT_3 antagonists for preventing PONV.[60-63] A recent study has also show that dexamethasone is at least as efficacious as granisetron and ondansetron at preventing PONV.[64]

The most common side effects of the 5-HT_3 receptor antagonists are constipation, headache, and asthenia, and the side effect profiles appear comparable. Safety and efficacy of palonosetron in children have not been established, while the other 5-HT_3 receptor antagonists are approved for the use in children. Granisetron and ondansetron are the only 5-HT_3 receptor antagonists that are available generically. No studies have been conducted that compare the efficacy and toxicity of brand 5-HT_3 receptor antagonist vs their respective generic alternatives. All of the 5-HT_3 receptor antagonists are available by injection and all but palonosetron are currently available by the oral route.

Therefore, all brand products within the class reviewed are comparable to each other and to the generic products in this class and offer no significant clinical advantage over other alternatives in general use. The 5-HT_3 antagonists are considered first-line therapy for special circumstances, such as patients receiving moderately to highly emetogenic chemotherapy or radiation therapy. Therefore, patients with a cancer diagnosis should be allowed approval of 5-HT_3 antagonists with quantity limits that correspond to anti-nausea regimens used for cancer chemotherapy.

Recommendations

In recognition of the following factors:

- the 5-HT_3 receptor antagonists (as a class) are considered part of the standard of care for patients receiving moderately to highly emetogenic chemotherapy
- current data suggests comparable safety and efficacy profiles of all agents in the class
- both ondansetron and granisetron are now available in generic form

…it is recommended that no changes be made to the current approval criteria aside from some slight rewording.

Aloxi, Anzemet, Granisetron, Kytril require prior authorization with the following approval criteria:

- The patient has had a documented side effect, allergy, or treatment failure to generic ondansetron. Additionally, after above trial, for approval of Kytril® injection, oral solution or tablets, generic granisetron injection, oral solution or tablets must have been tried.

- Anzemet has the following quantity limits: for nausea and vomiting associated with chemotherapy, 1 tablet for each day of chemotherapy and 1 tablet for each day on days 2-4 after chemotherapy may be approved.

- Kytril has the following quantity limits: for nausea and vomiting associated with chemotherapy, 2 tablets for each day of chemotherapy and 2 tablets for each day on days 2-4 after chemotherapy may be approved.

Zofran requires prior authorization with the following approval criteria:

- The patient must have a documented intolerance to the corresponding generic ondansetron product (tablets, orally disintegrating tablets (ODT), oral solution or injection).

Ondansetron oral solution requires prior authorization with the following approval criteria:

- The patient is unable to use ondansetron ODT or ondansetron tablets.

Ondansetron 24 mg tablet requires prior authorization with the following approval criteria:

- The prescriber provides rationale why generic ondansetron 8 mg tablets cannot be used to achieve the desired dose.

Ondansetron 4 mg and 8 mg tablets and ODTs are preferred when the following quantity limits are met:

- For nausea and vomiting associated with chemotherapy, 3 tablets for each day of chemotherapy and 3 tablets for each day on days 2-4 after chemotherapy may be approved.

- For hyperemesis gravadarum, three tablets per day of 4 mg or 8 mg may be approved for 3 months.

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